

Evaluation of the Toxicity of Organogermanium Compounds

Prepared by:

Gary J. Burin, MPH, Ph.D., DABT

**Technology Sciences Group Inc.
Washington DC
20036**

September 28, 2005

Executive Summary

Germanium is an ultratrace element found in many ordinary foods. Organic complexes of germanium have been proposed for use as dietary supplements and chemotherapeutic agents and have been well tested in laboratory animals. The results of repeat dose studies of these compounds show little or no toxicity, even at relatively high dose levels. This is in contrast to inorganic germanium compounds, such as germanium dioxide, which cause significant and irreversible renal toxicity at low dose levels in studies in laboratory animals and which has been associated with renal toxicity in humans. The few reports of toxicity in humans after the intake of dietary supplements containing organogermanium compounds have been subsequently attributed to the presence of germanium dioxide in the supplements. Unlike inorganic germanium, organogermanium compounds appear to have lower bioavailability and little potential to accumulate in renal tissue. A clear difference in toxicity between inorganic germanium and organogermanium compounds is apparent based upon this review of the available information in the scientific literature.

Introduction

Germanium makes up approximately 0.0007% of the earth's crust and many commonly consumed foods contain significant quantities of germanium with concentrations ranging from 5.76 ppm in canned tomato juice to 1.51 ppm in homogenized milk (Fisher and Goering, 1991). Inorganic germanium compounds have been found to induce anemia, muscle weakness and renal failure in humans and various forms of toxicity in laboratory animals (for a comprehensive review of the toxicity of inorganic germanium, see Tao and Bolger (1997)). The renal toxicity of inorganic germanium has been particularly well-studied and is known to be similar to that observed with other trace elements (Vanholder *et al.*, 2002). Low levels of trace elements such as germanium are eliminated from the body without the induction of any toxicity. Higher dose levels result in declining kidney function which, in turn, leads to the accumulation of nephrotoxic levels of the trace element, causing further deterioration of renal function (Vanholder *et al.*, 1996). The Lowest Observed Adverse Effect Levels (LOAELs) in humans for inorganic germanium toxicity have been reported to range from 0.7 to 23 mg/kg bw/day (Tao and Bolger, 1997).

The following summary of toxicity and clinical information, with particular attention placed upon renal toxicity, was prepared to contrast the toxicity of organogermanium and inorganic germanium compounds.

Review of Available Toxicity Information for Organogermanium Compounds

Toxicity Studies in Rats

Anger *et al.*, (1992) found that dosing of 15 male and 15 female Wistar rats at a single dose of 1 g/kg bw/day of carboxyethylgermanium sesquioxide¹ in the diet for six months resulted in no clinical signs of toxicity and no treatment-related mortality. The highest

¹ Also known as Ge-132, propagermanium and SK-818.

level of germanium was detected in the kidney with a concentration of 1.86 ppm being found at the end of six months. Although the limit of detection was not reported, levels as low as 0.08 ppm were reported in other tissues. No detectable germanium was found in control animals. Kidney lesions were noted upon microscopic examination and consisted of "widening of the cylinders and some flocculus deposits". These lesions were observed in about 60% of treated males, but not in females. Evidence of renal dysfunction in males, in the form of a slight increase in serum creatinine and a decrease in serum proteins, was also noted. The authors concluded that the study confirmed the low toxicity of organic germanium in comparison with inorganic germanium. They also cited data showing poor oral bioavailability (2.6%) of the organic germanium compared with 10% oral bioavailability for the inorganic form.

In a related report, Anger *et al.*, (1991) summarized the results of the study discussed above and included findings from a 28-day study in Wistar rats that was conducted in conjunction with the six-month study. No macroscopic or histological changes were seen after 28 days of administration of one g/kg bw/day to 15 male and 15 female Wistar rats. The authors reported a slight decrease of erythropoiesis and a stimulation of general metabolism in treated animals.

Asano *et al.*, (1994) compared the renal toxicity of propagermanium and germanium dioxide administered in drinking water for eight weeks to male Wistar rats. Propagermanium was administered at concentrations of 480 or 2,400 ppm (equivalent to approximately 192 mg/kg bw/day) and germanium dioxide was administered at concentrations of 300 or 1,500 ppm (equivalent to approximately 120 mg/kg bw/day). Treated groups consisted of 13 rats and the control groups contained 9 rats with three animals per group sacrificed after 3 weeks. Rats were intravenously administered 3 mg/kg adriamycin to induce kidney injury. Alterations in the form of vacuolization and deposits were observed in the distal tubule in germanium dioxide-treated rats but not in propagermanium-treated rats. The authors concluded that propagermanium, at the dose levels administered, does not induce renal toxicity or exacerbate renal toxicity that is already present.

The toxicities of propagermanium and germanium dioxide after repeat dosing were also investigated by Sanai *et al.*, (1991). Female Wistar rats were divided into three groups of 16 to 20 rats and these groups received diet containing either 75 mg/kg bw/day of germanium dioxide, 120 mg/kg bw/day of Ge-132 or control diet for 24 weeks. The dose levels were selected to provide equal dose levels of germanium. Approximately one-third of the animals in each group were sacrificed after 24 weeks of dosing or after an additional 2 or 14 week withdrawal period. No indications of toxicity were found in any of the animals receiving Ge-132. In contrast, anemia, body weight loss, and various serum, urinalysis and histological indications of renal toxicity were seen in the animals receiving germanium dioxide. The histological lesions in this group were characterized as vacuolar degeneration and granular depositions in the distal tubules of the kidney. Renal toxicity induced by germanium dioxide persisted until the 40 week sacrifice. Lower renal concentrations of germanium were found in Ge-132-treated rats than in those rats receiving germanium dioxide. The investigators concluded that "Our present study

demonstrated that Ge-132 had extremely low toxicity.” A previous review of a large body of toxicological and pharmacological literature concerning Ge-132 concluded that “Ge-132 appeared to be almost non-toxic in all of the animal studies performed” (Brutkiewicz and Suzuki, 1987).

Kandra *et al.*, (1990), summarized in Tao and Bolger (1997), noted a variety of forms of toxicity in rats after the administration of 1600 mg/kg bw/day and greater of the organogermanium compound, SK-818. Dilated and “rarefied wall” cecum were reported at 640 mg/kg bw/day. Nakagawa *et al.*, (1990), also summarized in Tao and Bolger (1997), found no renal toxicity of SK-818 at a dose level of 750 mg/kg bw/day in rats after dosing for one year.

A study of organogermanium toxicity in rats was reported by Ahn *et al.*, (2001). Ten Sprague-Dawley rats per sex were fed diets containing Dry Yeast G (0.3% germanium), at concentrations resulting in either 50, 500 or 5,000 mg/kg bw/day, equivalent to 0.15, 1.5, or 15 mg/kg bw/day of germanium, for 10 months. Urinalysis, hematology, clinical chemistry, clinical observations and histological examinations of a variety of organs, including the kidney, were conducted. There were no changes in any parameter and the NOAEL was therefore 15 mg/kg bw/day for the organic form of germanium that was administered in the diet in this study.

In contrast to the previous studies of organogermanium compounds, Taylor *et al.*, (1991) reported in abstract that germanium dioxide, germanium sesquioxide and peptide-bound germanium were all similarly toxic when administered to Wistar albino rats for up to six weeks. All animals (number per group not specified) received 50 micrograms of germanium per gram of food (equivalent to 5 mg/kg bw/day). Although germanium was reportedly found in all tissues that were examined, the concentration in the kidneys (the tissue with the highest concentration) of rats treated with germanium dioxide and germanium sesquioxide were similar to the control animals (0.067, 0.036 and 0.050 ug/g for the germanium dioxide, germanium sesquioxide and peptide-bound germanium groups, respectively). Urinary excretion of germanium was 4.3, 50.0 and 23.8 micrograms per day for the same three groups, suggesting impaired excretion of the germanium in the animals administered germanium dioxide but no effect on excretion in animals administered germanium sesquioxide. The reduced excretion in the animals receiving peptide-bound germanium is most likely due to reduced bioavailability. The histological changes reported consisted of enlarged nuclei with homogenous internal structure, swollen mitochondria and budding of the cytoplasm into the tubular lumen in distal tubular cells. Surprisingly, no changes were reported in serum creatinine or urea, or protein in the urine. Although the histological changes were “consistent” in all three groups it is not clear why functional changes were not observed. It appears that only one animal was examined histologically in each treated group and it is unclear why functional changes did not correlate with the histological observations.

Toxicity Studies in Dogs

Beagle dogs were administered biogermanium yeast dissolved in water (Ahn *et al.*, 2001) for ten months. Dose levels were 1.5, 15 and 150 mg/kg bw/day of Dry Yeast G (0.3% germanium), equivalent to 0.0045, 0.045 and 0.45 mg/kg bw/day of germanium, were given to five animals at each dose level. Urinalysis, hematology, clinical chemistry, clinical observations and histological examinations of a variety of organs, including the kidney, were conducted. There were no changes in any parameter and the NOAEL in beagle dogs was therefore 0.45 mg/kg bw/day for this organic form of germanium.

In vitro Studies

Spirogermanium inhibits DNA, RNA and protein synthesis *in vitro* (Yang and Raflah, 1983). Cytolysis is observed at high concentrations. Both mutagenic and antimutagenic properties of organogermanium compounds have been reported in the open literature (see Gerber and Leonard, 1997).

Carcinogenicity and Genotoxicity Studies

The same authors (Gerber and Leonard, 1997) also report that antineoplastic effects have been associated with the administration of organogermanium compounds in rodents. The organogermanium compound Ge-132 was found to increase interferon activity and NK cell activity in mice following oral administration of 300 mg/kg bw/day (Asao *et al.*, 1985).

Clinical Studies and Case Reports in Humans

Various organogermanium compounds have been investigated as chemotherapeutic agents in humans, and there are case reports of toxicity in humans after high intakes of organogermanium dietary supplements. However, these reports are of limited value due to the high dose levels and uncertain purities of the administered substances. Many of the clinical studies used the intravenous route of administration and the few foreign reports of toxicity following the intake of dietary supplements did not provide adequate characterization of the supplements. The four reported cases of renal toxicity after the intake of the organogermanium compound germanium-lactate-citrate were later found to be due to the intake of inorganic germanium (see Tao and Bolger, 1997).

Conclusions

The toxicity of organogermanium compounds has been evaluated in several studies in laboratory animals. Rats show no indications of renal or other toxicity at dietary dose levels of up to 192 mg/kg /day. Dose levels of organogermanium compounds associated with renal or other forms of toxicity range from 640 mg/kg /day to 1,000 mg/kg /day. A single report, in the form of an abstract, of histological evidence of organogermanium renal toxicity in rats at a dose level as low as 5 mg/kg /day is not consistent with the evidence available from other studies and lacks sufficient detail to allow critical evaluation.

The high dose levels of organogermanium necessary to induce toxicity are in contrast to inorganic germanium, which has shown to induce renal toxicity at dose levels of 75 mg/kg /day in rodents and 0.7 to 23 mg/kg /day in case reports of human toxicity with no indication of a clear No Observed Adverse Effect Level (NOAEL) being apparent in humans or laboratory animals. The relative lack of toxicity of organogermanium compounds appear to be due to a lower bioavailability and a reduced potential for accumulation in the kidney compared with the more toxic inorganic germanium.

Although toxicity from the intake of organogermanium compounds by humans has been reported in the scientific literature, subsequent investigations have found the toxicity to be due to the intake of inorganic germanium. Organogermanium compounds appear to be of little toxicological concern.

Table: Summary of Organogermanium Toxicity Studies in Laboratory Animals

Test Material	Species/strain (sex)	Duration	NOAEL or Max. Dose Level	Results	Reference
Carboxylethyl germanium sesquioxide	Wistar rats (male and female)	Six months	One gram/kg bw/day	Moderate renal toxicity in males only	Anger <i>et al.</i> , 1992
Carboxylethyl germanium sesquioxide	Wistar rats (male and female)	28 days	One gram/kg bw/day	Clinical chemistry alterations	Anger <i>et al.</i> , 1991
Carboxylethyl germanium sesquioxide	Wistar rats (male)	Eight weeks	192 mg/kg/day	No toxicity	Asano <i>et al.</i> , 1994
Carboxylethyl germanium sesquioxide	Wistar rats (females)	24 weeks	120 mg/kg/day	No toxicity	Sanai <i>et al.</i> , 1991
Carboxylethyl germanium sesquioxide	Rats, unknown strain and sex	Three months	640 mg/kg/day (lowest dose tested)	Dilated cecum and "rarefied wall"	Kandra <i>et al.</i> , 1990
Carboxylethyl germanium sesquioxide	Rat, unknown strain and sex	One year	750 mg/kg/day	No renal toxicity	Nakagawa <i>et al.</i> , 1990
Biogermanium	Sprague-Dawley rats, males and females	Ten months	5,000 mg/kg/day, equivalent to 15 mg/kg/day germanium	No toxicity	Ahn <i>et al.</i> , 2001
Germanium sesquioxide and peptide-bound germanium	Wistar rats, unknown sex	Six weeks	Equivalent to 5 mg/kg/day	Renal toxicity	Taylor <i>et al.</i> , 1991
Biogermanium	Beagle dogs, males and females	Ten months	150 mg/kg/day, equivalent to 0.45 mg germanium	No toxicity	Ahn <i>et al.</i> , 2001

References

- Ahn *et al.*, 2001
Anger *et al.*, 1991
Anger *et al.*, 1991
Asano *et al.*, 1994
Asao *et al.*, 1985
Brutkiewicz and Suzuki, 1987
Fisher and Goering, 1991
Gerber and Leonard, 1997
Kandra *et al.*, 1990
Nakagawa *et al.*, 1990
Sanai *et al.*, 1991
Tao and Bolger, 1997
Taylor *et al.*, 1991
Vanholder *et al.*, 1991
Vanholder *et al.*, 1996
Yang and Raflah, 1983